Comparison of fleroxacin and penicillin G plus probenecid in the treatment of acute uncomplicated gonococcal infections

A Lassus, L Abath Filho, M F Queiros Santos Junior, L Belli

Abstract

***Objective*—To investigate the activity of fleroxacin in acute uncomplicated infections with *N. gonorrhoeae* in comparison with conventional penicillin G plus probenecid treatment.**

***Design*—Multicentre open label randomised parallel group study.**

***Subjects*—Male patients aged 18 years or over from university departments of urology, epidemiology and dermatology and a clinic for sexually transmitted diseases.**

***Interventions*—Two hundred and sixty male patients were randomly assigned to treatment with either a single oral dose of fleroxacin 400 mg (130 patients) or a single intramuscular dose of penicillin G (2·4 or 5·0 mega units) plus a single oral dose of probenecid 1 gram (130 patients). Efficacy and safety assessments were undertaken at follow-up (3–14 days after treatment). Efficacy was assessed as bacteriological outcome of treatment. Safety was assessed by evaluation of adverse events, laboratory abnormalities and changes in vital signs.**

***Results*—Two hundred and twenty four patients (114 in the fleroxacin group and 110 in the penicillin plus probenecid group) were evaluated for efficacy. Bacteriological cures were achieved in 100% of patients in the fleroxacin group and 97% of patients in the penicillin plus probenecid group. There was no statistically significant difference between the two groups in this respect (Fisher exact test, p = 0·25). Clinical cures were achieved in 100% of patients receiving fleroxacin and 95% of patients receiving penicillin plus probenecid. Safety analyses were undertaken on 255 patients (126 in the fleroxacin group and 129 in the penicillin plus probenecid group). No adverse events were reported for either treatment group, and no clinically relevant laboratory abnormalities were apparent. Thus, there appeared to be no difference in the efficacy or safety of these two treatments when used to treat acute, uncomplicated urethral gonorrhoea in males.**

***Conclusions*—In this study fleroxacin proved to be highly effective therapy for uncomplicated gonococcal urethritis in males and may provide a favourable alternative to standard treatment.**

Dermatology Department, Helsinki University Central Hospital, 170 Helsinki, Finland
A Lassus

Urological Department, University Hospital Da Paraiba, 508059 Joao Pessoa, Brazil
L Abath Filho

Epidemiology Department, Av Dr Arnaldo 715, 1255 Sao Paulo, Brazil
M F Queiros Santos Junior

Department for Sexually Transmitted Diseases, Hospital Jose de San Martin, 1120 Buenos Aires, Argentina

Address for correspondence: Professor A Lassus, Ars Medicina, Iso Roobertinkatu 8A, 00120 Helsinki, Finland

Accepted for publication 27 May 1992

Introduction

Drug therapy for *Neisseria gonorrhoeae* infections has undergone many changes since the introduction of sulphonamide over 50 years ago. Following the rapid development of resistance to this drug, penicillin therapy, introduced in the 1940s, proved to be a timely alternative.[1] However, gonococcal strains that were less susceptible to penicillin emerged around 1957, and treatment failures became more common. Since then, both penicillin-resistant strains (penicillinase-producing *N. gonorrhoeae,* PPNG) and strains resistant or less susceptible to a range of antibacterial agents (chromosomally-mediated resistant *N. gonorrhoeae,* CMRNG; tetracycline-resistant *N. gonorrhoeae,* TRNG) have developed,[2 3] reducing the efficacy of conventional drug treatments.

A variety of alternatives, including members of the quinolone family such as ciprofloxacin and norfloxacin, have been proposed to overcome the problems of resistance and decreased susceptibility to standard therapy.[4 5] The new fluoroquinolone, fleroxacin, may be a useful additional therapeutic agent.

Fleroxacin has been shown to have good in vitro antibacterial activity against a wide range of organisms, and its in vivo efficacy is comparable to that of other quinolones, such as ciprofloxacin, enoxacin, norfloxacin and ofloxacin.[6–8] Against *N. gonorrhoeae,* various MIC_{90} values for fleroxacin in vitro have been reported, from $\leqslant 0{\cdot}015\ \mu g/ml$[6] and $\leqslant 0{\cdot}13\ \mu g/ml$[7] to $\leqslant 0{\cdot}5\ \mu g/ml$[8]. Fleroxacin has also been tested on non-PPNG, PPNG and CMRNG strains, resulting MIC_{90} values being 0·03 mg/l, 0·03 mg/l and 0·06 mg/l, respectively.[9]

The purpose of this study was to investigate the activity of fleroxacin in vivo against acute, uncomplicated gonococcal infections, in comparison with a conventional treatment (penicillin G plus probenecid).

Methods

Patient population

Patients were recruited to this study from those receiving treatment at university departments of urology, epidemiology and dermatology, and a clinic for sexually transmitted diseases. Individuals were included in the study if they were male, aged 18 years or over, with a diagnosis of acute, uncomplicated urethral gonococcal infections. The presence of typical intracellular Gram-negative diplococci in a urethral smear was taken as the initial diagnosis criterion; this was confirmed by a sample culture within 48 hours of treatment com-

mencing.

Patients agreed to refrain from sexual intercourse throughout the duration of the study, until after the follow-up visit. All patients recruited to the trial gave written or oral informed consent before treatment began.

Individuals were excluded from the trial if they had systemic complications of gonococcal infections (for example septicaemia or arthritis); if they had serious concomitant disease (such as severe renal or hepatic insufficiency) or a history of cerebral attacks; if reinfection during the trial period could not be excluded; if they received concomitant antimicrobial therapy during the trial, or successful antimicrobial therapy up to seven days before enrolement; or if they appeared unwilling or unable to accept the requirements of the study.

Study design

This was an open-label, randomised, parallel group, multicentre study. Each patient fulfilling the selection criteria underwent baseline assessments as follows: a medical history and demographic details recorded, a physical examination undertaken, and a blood sample taken (to test for concomitant venereal disease). In addition, blood and urine samples were taken for laboratory safety tests, and urethral, rectal and pharyngeal samples taken for bacteriological culture within 48 hours of treatment commencing.

Patients were then randomised to one of two treatment groups: either a single oral dose of fleroxacin 400 mg, or a single intramuscular injection of penicillin G (2·4 MU at 3 centres; 5 MU at 1 centre) plus a single oral dose of probenecid 1 g. Follow-up clinical, bacteriological and laboratory safety assessments were carried out 3 to 14 days after the treatment day.

The presence of a susceptible pathogen up to 48 hours before treatment began was a prerequisite for valid bacteriological assessment. All *Neisseria species* isolated before treatment were tested for susceptibility to fleroxacin and penicillin G by in vitro disc diffusion or MIC criteria.

Table 1 Summary of demographic data of patients evaluated for efficacy

Parameter	*Fleroxacin p.o. 400 mg n = 114*	*Penicillin i.m. 2·4 or 5 MU n = 110*
Sex:	114 (100%)	110 (100%)
Males		
Females	—	—
Age at treatment (years):		
Mean	27	27
SD	7	7
Median	25	26
Range	18–61	18–47
Weight (kg):		
Mean	70	72
SD	8	10
Median	70	71
Range	48–100	48–115
Height (cm):		
Mean	174	174
SD	7	7
Median	175	175
Range	157–187	157–190
Race:		
White	103 (90%)	99 (90%)
Black	8 (8%)	9 (8%)
Oriental	3 (2%)	1 (1%)
Other	—	1

Efficacy and safety evaluations

Bacteriological outcome was the primary efficacy parameter and was determined by the assessment of *N. gonorrhoeae* for each infection. Failure was defined as presence of the original causative pathogen in at least one culture at follow-up; cure was defined as no failure and elimination of the causative pathogen from cultures at follow-up.

Clinical outcome was assessed as cure (absence of clinical symptoms), improvement, failure (no apparent response to treatment), or not assessable (where a clinical judgement could not be made).

Safety was assessed by the number and severity of adverse events and their relationship to treatment, and marked abnormalities in

Results

A total of 260 patients from four centres entered into this study; 130 were randomised to fleroxacin treatment and the remaining 130 were randomised to penicillin plus probenecid treatment. One patient in each group was not evaluated at follow-up as they failed to return after treatment. Three patients were re-entered into the study and were excluded from efficacy and safety populations for their second treatment (which was fleroxacin in all the three cases). Thus, 126 patients (fleroxacin group) and 129 patients (penicillin plus probenecid group) were evaluated in the safety analysis.

The total numbers of patients included in the analysis of efficacy were 114 in the fleroxacin group and 110 in the penicillin plus probenecid group. The main reason for exclusion was the absence of a pre-therapy susceptibility test in the fleroxacin group; and the resistance of the causative pathogen to the drug given in the other treatment group.

Demographic details of those patients evaluated in the efficacy analysis are given in table 1. Demographic parameters for both groups were comparable.

Baseline clinical signs and symptoms in each treatment group are shown in table 2. The two groups were comparable in terms of the nature and severity of these parameters. The most common symptoms in each group and each efficacy population were purulent discharge and dysuria. All patients enrolled in the study were examined at baseline for rectal and pharyngeal gonorrhoea; no patients presented with rectal gonorrhoea and only one patient had pharyngeal gonorrhoea.

Few patients reported concomitant diseases or conditions. The most commonly reported concomitant conditions were mental disorders (alcohol, nicotine or drug abuse). These affected 4% of patients in the fleroxacin group and 2% of the penicillin plus probenecid group. Both groups were comparable in this respect. Only one patient (in the fleroxacin group) received concomitant medication during the trial (nifedipine for hypertension).

Table 2 Summary of baseline status of clinical signs and symptoms of infection

Sign/sympton	Fleroxacin p.o. 400 mg n = 114	Penicillin i.m. 2·4 or 5 MU n = 110
Dyruria	9 (8%)	6 (5%)
None/absent		
Mild	34 (30%)	31 (28%)
Moderate	51 (45%)	54 (49%)
Severe	20 (18%)	19 (17%)
Flank tenderness		
None/absent	70 (61%)	71 (65%)
Mild	11 (10%)	11 (10%)
Moderate	32 (28%)	27 (25%)
Severe	3 (1%)	1 (1%)
Prostatic tenderness		
None/absent	114 (100%)	99 (99%)
Mild/absent	—	1 (1%)
Moderate	—	—
Severe	—	—
Purulent discharge		
None/absent	—	—
Mild	24 (21%)	17 (15%)
Moderate	56 (49%)	53 (48%)
Severe	34 (30%)	40 (36%)
Skin swelling		
None/absent	56 (49%)	65 (59%)
Mild	39 (34%)	29 (26%)
Moderate	18 (16%)	16 (15%)
Severe	1 (1%)	—

Bacteriological outcome

Bacteriological cure was achieved in 114 patients (100%; with 95% confidence limits 96–100%) in the fleroxacin group, and 110 patients (97%; with 95% confidence limits 92–99%) in the penicillin plus probenecid group. There was no statistically significant difference in bacteriological outcome between the two groups (Fisher Exact Test, p = 0·25).

Clinical outcome

A summary of the investigators' assessments of clinical outcome is given in table 3. In the fleroxacin group all 114 patients (100%) were reported to be cured, and in the penicillin plus probenecid group 105 patients (5%) were reported to be cured. No statistically significant difference in clinical outcome was found (Fisher Exact Test, p = 0·17).

Safety

A total of 255 patients were evaluated for safety parameters. No adverse events, serious or otherwise, were reported in either of the two treatment groups; the three patients who re-entered the study reported no adverse events after the second exposure. Six patients (four in the fleroxacin group and two in the penicillin plus probenecid group) exhibited marked laboratory abnormalities (six values) from the investigator's normal range. Only one (in the penicillin plus probenecid group) was rated as being related to treatment (remotely), that of a total bilirubin value at follow-up higher than the baseline value. However, the baseline value of this patient was above the investigator's normal range. No marked laboratory abnormalities were evident in the three patients who re-entered the study after the second exposure.

No clinically relevant abnormalities in vital signs were found.

Table 3 Summary of investigator's assessments of clinical outcome

Response rating	Fleroxacin p.o. 400 mg n = 114	Penicillin i.m. 2·4 or 5 MU n = 110
Infection: Urethral gonorrhea		
No of patients	114	110
Cure	114 (100%)	105 (95%)
Improvement	—	2 (2%)
Failure	—	3 (3%)
Not assessable	—	—

Discussion

Many different antibacterial agents have been used effectively to treat gonococcal infections, as reflected in the literature.[10–14] However, drug therapy has had to respond to the problems posed by the progressive development of resistance in *N. gonorrhoeae* and its decreasing susceptibility to some of these previously effective compounds. Of the newer drugs that are being proposed for treatment of gonorrhoea, the fluoroquinolones appear to be particularly promising. Single oral doses of ciprofloxacin, norfloxacin, ofloxacin and enoxacin have all been shown to produce cure rates of close to 100% in both males and females.[4 15] These cure rates compare well with those obtained with cephalosporins and other compounds such as ampicillin and amoxicillin.[4]

The changing views on effective drug therapy for gonorrhoea is reflected in the World Health Organisation changing its standard recommended regimen for *N. gonorrhoeae* infections. In 1983 the recommended regimen was either a single injectable or oral dose of penicillin plus probenecid or a course of tetracycline. Now, the recommended regimen is a single dose of ceftriaxone 250 mg i.m., ciprofloxacin 500 mg p.o. or spectrinomycin 2 g i.m.[5]

In the study reported here, the efficacy of the new fluoroquinolone fleroxacin was compared with that of penicillin plus probenecid. The results demonstrated that a single oral dose of fleroxacin 400 mg was sufficient to produce high bacteriological and clinical cure rates (100% in both cases) in 114 male patients with acute, uncomplicated urethral gonococcal infections. These results were obtained 3–14 days after treatment, indicating a rapid onset of action of the drug. In comparison, a single intramuscular injection of penicillin G (2·4 or 5 MU) plus a single oral dose of probenecid 1 g resulted in a bacteriological cure rate of 97% and a clinical cure rate of 95% in 110 patients. Although the treatment failures were in this group, there was no statistical difference between the two drug treatments with regard to efficacy, either assessed by bacteriological outcome (Fisher Exact Test, p = 0·25) or clinical outcome (Fisher Exact Test, p = 0·17).

In both groups, the *N. gonorrhoeae* isolates obtained prior to commencement of the study were tested for susceptibility to the test drugs. Twenty-four of the 247 isolates obtained (9·7%) were found to be resistant to penicillin G, whereas none was resistant to fleroxacin. Only those individuals in which the causative pathogen judged to be susceptible to the test

drug to which the patient was randomised were included in the analysis of efficacy. This observed resistance to penicillin but not to fleroxacin is further evidence of the potential for fleroxacin as an effective treatment for gonococcal infections.

Both drug treatments were well tolerated. None of the 255 patients assessed for safety reported any adverse events laboratory abnormalities or clinically relevant abnormalities in vital signs, related to treatment.

Evidence from this and other studies supports the view that fleroxaxin and other fluoroquinolones are highly effective single dose therapies for gonococcal infections. From the point of view of patient compliance they are easier to administer than alternative treatments (being orally active), require the administration of only a single dose, and have a low incidence of adverse events.[4 16] From a bacteriological point of view, they are effective against PPNG strains and other resistant strains of *N. gonorrhoeae*, as shown in this and other studies.[16] Fleroxacin, in particular, has the advantage of having a long elimination half-life (9·7 h), and the orally administered drug is excreted in high concentrations in urine in its active form,[17] supporting its use in gonococcal urethritis.

In conclusion, fleroxacin appears to be a highly effective treatment for uncomplicated urethral gonorrhoea, and may provide a favourable alternative to standard treatments.

1 Lind I. Epidemiology of antibiotic resistant Neisseria gonorrhoeae in industrialized and developing countries. *Scand J Infect Dis* 1990;**69**:77–82.

2 Ison CA, Bindayna KM, Woodford N, Gill MJ, Easmon CSF. Penicillin and cephalosporin resistance in gonococci. *Genitourin Med* 1990;**66**:351–6.

3 Danielsson D. Gonorrhea: diagnostic and therapeutic strategies in the era of resistance to antibiotics. *Seminars in Dermatology.* 1990;**9**:109–16.

4 Moran JS, Zenilman JM. Therapy for gonococcal infections: options in 1989. *Rev Infect Dis.* 1990;**12(suppl 6)**: S633–S644.

5 Easmon CSF. The changing pattern of antibiotic resistance of Neisseria gonorrhoeae. *Genitourin Med* 1990;**66**:55–6.

6 Chin N-X, Brittain DC, Neu HC. In vitro activity of Ro 23–6240, a new fluorinated 4-quinolone. *Antimicrob Agents Chemother* 1986;**29**:675–80.

7 Fuchs PC, Jones RN, Barry Al, *et al.* Ro 23–6240 (AM-833), a new fluoroquinolone: in vitro antimicrobial activity and tentative disk diffusion interpretive criteria. *Diagn Microbiol Infect Dis* 1987;**7**:29–35.

8 Manek N, Andrews JM, Wise R. In vitro activity of Ro 23–6240, a new difluoroquinolone derivative, compared with that of other antimicrobial agents. *Antimicrob Agents Chemother* 1986;**30**:330–2.

9 van der Willigen AH, Degener JE, Vogel M, Stolz E, Wagenvoort JHT. In vitro activities of seven quinolone derivatives against Neisseria gonorrhoeae. *Arzneimittel-Forschung.* 1990;**40**:684–5.

10 Karney WW, Turck M, Holmes KK. Session VIII. Treatment of gonococcal infections with amoxicillin. Single-dose oral therapy for uncomplicated gonorrhea: comparison of amoxicillin and ampicillin given with and without probenecid. *J Infect Dis* 1975;**129(suppl)**:S250–S253.

11 Braithwaite AR. Double-blind trial of amoxycillin and ampicillin plus probenecid in the treatment of gonorrhoea in men. *Br J Venereal Dis* 1979;**55**:340–2.

12 Lassus A, Renkonen O-V. Short-term treatment of gonorrhoea with intramuscular and oral forms of trimethoprim-sulphamethoxazole. *Br J Venereal Dis* 1979;**55**:24–5.

13 Mohanty KC, Fimls RD, Strachan RG. A comparative study of aztreonam and procaine penicillin/probenecid in the treatment of uncomplicated gonorrhoea. *Scand J Infect Dis* 1988;**20**:33–6.

14 Veeravahu M, Clay JC, Mohanty KC, Tovey SJ, Wanas TM, Roberts KN. Efficacy of ceftizoxime in the treatment of uncomplicated gonorrhoea: comparison with amoxycillin. *Br J Clin Practice* 1990;**44**:216–18.

15 Paton JH, Reeves DS. Fluoroquinolone antibiotics. Microbiology, pharmacokinetics and clinical use. *Drugs* 1988; **36**:193–228.

16 Covino JM, Cummings M, Smith B, Benes S, Draft K, McCormack WM. Comparison of ofloxacin and ceftriaxone in the treatment of uncomplicated gonorrhea caused by penicillinase-producing and non-penicillinase-producing strains. *Antimicrob Agents Chemother* 1990;**34**: 148–9.

17 Weidekamm E, Portmann R, Suter K, Partos C, Dell D, Lücker PW. Single- and multiple-dose pharmacokinetics of fleroxacin, a trifluorinated quinolone, in humans. *Antimicrob Agents Chemother* 1987;**31**:1909–14.